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Inhaled sodium cromoglycate for asthma in children

van der Wouden, Johannes C.; Uijen, Johannes H. J. M.; Bernsen, Roos M. D.; Tasche, Marjolein J. A.; de Jongste, Johan C.; Ducharme, Francine

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Inhaled sodium cromoglycate for asthma in children (Review)

van der Wouden JC, Uijen JHJM, Bernsen RMD, Tasche MJA, de Jongste JC, Ducharme FM

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Inhaled sodium cromoglycate for asthma in children

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ABSTRACT

Background

Sodium cromoglycate has been recommended as maintenance treatment for childhood asthma for many years. Its use has decreased since 1990, when inhaled corticosteroids became popular, but it is still used in many countries.

Objectives

To determine the efficacy of sodium cromoglycate compared to placebo in the prophylactic treatment of children with asthma.

Search methods

We searched the Cochrane Airways Group Trials Register (October 2009), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2009), MEDLINE (January 1966 to October 2009), EMBASE (January 1985 to October 2009) and reference lists of articles. We also contacted the pharmaceutical company manufacturing sodium cromoglycate.

Selection criteria

All double-blind, placebo-controlled randomised trials, which addressed the effectiveness of inhaled sodium cromoglycate as maintenance therapy, studying children aged 0 up to 18 years with asthma.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. We pooled study results.

Main results

Of 3500 titles retrieved from the literature, 24 papers reporting on 23 studies could be included in the review. The studies were published between 1970 and 1997 and together included 1026 participants. Most were cross-over studies. Few studies provided sufficient information to judge the concealment of allocation. Four studies provided results for the percentage of symptom-free days. Pooling the results did not reveal a statistically significant difference between sodium cromoglycate and placebo. For the other pooled outcomes, most of the symptom-related outcomes and bronchodilator use showed statistically significant results, but treatment effects were small. Considering the confidence intervals of the outcome measures, a clinically relevant effect of sodium cromoglycate cannot be excluded. The funnel plot showed an under-representation of small studies with negative results, suggesting publication bias.

Authors' conclusions

There is insufficient evidence to be sure about the efficacy of sodium cromoglycate over placebo. Publication bias is likely to have overestimated the beneficial effects of sodium cromoglycate as maintenance therapy in childhood asthma.

PLAIN LANGUAGE SUMMARY

The effects of sodium cromoglycate compared with placebo for chronic asthma in children

In this review we aimed to determine whether there is evidence for the effectiveness of inhaled sodium cromoglycate as maintenance treatment in children with chronic asthma. Most of the studies were carried out in small groups of patients. Furthermore, we suspect that not all studies undertaken have been published. The results show that there is insufficient evidence to be sure about the beneficial effect of sodium cromoglycate compared to placebo. However, for several outcome measures the results favoured sodium cromoglycate.

BACKGROUND

Since the late 1960s, disodium cromoglycate (DSCG) has been used as maintenance treatment for children with moderate asthma, although the precise mechanism of action is still not fully understood. No serious side effects have been reported in trials, but cases of dysuria, urticaria, bronchospasm, angio-oedema and anaphylaxis have been ascribed to the use of DSCG, once with death as a result (Lester 1997; Leynadier 1985).

In the early 1990s, many guidelines recommended use of DSCG. Gradually, corticosteroids have come to the fore as first choice maintenance therapy (BAG 1997; Ernst 1996), or were recommended alongside DSCG for mild persistent asthma (NIH 1997). Other guidelines continued to recommend DSCG as first choice in young children (Sly 1997). The most recent revisions of the GINA and NIH guidelines (GINA 2005; NIH 2002) consider the role of DSCG in children to be limited. Inhaled glucocorticosteroids are the first choice; DSCG is only recommended as one of the alternative treatment options for children with mild persistent asthma. Canadian guidelines no longer recommend DSCG as maintenance therapy for children, nor do British guidelines for children aged 5 to 12 years (Becker 2005; BTS 2003, page i20).

The long-term side effects of asthma treatment with inhaled steroids in early childhood are not clear. Nevertheless, there is concern that treating very mild cases of asthma with inhaled steroids may have an adverse effect on the balance between risk and benefit. A Cochrane review has shown an effect of inhaled beclomethasone on linear growth in children (Sharek 1999). Therefore, physicians involved in the treatment of asthma in children may still prefer sodium cromoglycate as first choice maintenance treatment.

The use of DSCG has decreased since 1990, while the use of

inhaled corticosteroids is increasing. The discrepancy between guidelines and the debate on the role of DSCG, which led to its recent withdrawal as first line maintenance treatment in young children in some countries, was the rationale to review the efficacy of inhaled DSCG as maintenance treatment for chronic childhood asthma.

OBJECTIVES

To determine whether there is evidence for the efficacy of inhaled sodium cromoglycate as maintenance treatment in children with asthma.

METHODS

Criteria for considering studies for this review

Types of studies

All double-blind, placebo-controlled, randomised clinical trials, which addressed the effectiveness of DSCG as maintenance therapy.

Types of participants

Children aged 0 up to 18 years with asthma in all settings (general practice, emergency departments, outpatient departments, hospitalised). We only included studies including both children and adults when results for children were presented separately. When

the number of children in these studies was less than five, we did not include the study.

Types of interventions

Inhaled sodium cromoglycate, delivered via any device: nebulised, by Spinhaler or by metered dose inhaler, with or without holding chamber. We only included trials that compared DSCG with placebo. No co-interventions were permitted other than rescue medication as needed.

Types of outcome measures

Primary outcomes

The primary outcome measure was the difference in percentage of days without asthma symptoms, between placebo and cromoglycate treatment.

Secondary outcomes

- Symptom scores (day cough, day wheeze, daytime asthma score, day activity, night cough, night wheeze, night-time asthma score, sleep disturbance, overall symptom/severity score)
- Auscultation score
- Preference of patients/parents and clinicians
- Overall success rate
- Bronchodilator use, use of oral steroids, hospital admission
- Side effects

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see the [Airways Group Module](#) for further details).

Additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2009), MEDLINE (January 1966 to October 2009) and EMBASE (1979 to October 2009) were also conducted. For MEDLINE and EMBASE we used the Cochrane sensitive search strategy to select all RCTs ([Dickersin 1994](#)) and in all databases, we used the following search terms:

cromolyn* OR dscg OR cromoglycate* or cromoglicate* OR cromone* or intal*

Searches are current to October 2009.

Searching other resources

We contacted the pharmaceutical company manufacturing DSCG (Rhône-Poulenc-Rorer, formerly Fisons plc, Loughborough, UK), checked bibliographies of retrieved trials and contacted primary authors of trials published after 1990 for any additional trials.

Data collection and analysis

Data extraction and management

Two authors extracted data. When using symptom scores, most studies used a scale of 0 to 3 points; where a different scale was used we transformed the mean and standard deviation for our purposes. We calculated confidence intervals for the treatment effect (difference in symptom score) for individual studies assuming a t-distribution.

Assessment of risk of bias in included studies

Two authors independently scored the methodological quality of all trials using three sets of criteria: Chalmers ([Chalmers 1981](#)), Jadad ([Jadad 1996](#)) and the Cochrane criteria for concealment. A third author determined the final decision if there was lack of consensus. Trials in which one of the authors was involved were also scored by an impartial author. We did not contact authors of the trials for confirmation of methodology and data extraction, because most of the studies were performed many years ago and we considered it unlikely that this would provide further useful information. When updating the review in 2007, a 'Risk of Bias' table was added (Figure 1).

Dealing with missing data

If no standard error of the treatment effect of a particular outcome measure was available, and could not be calculated, we imputed it from a study with a similar design (cross-over or parallel) (cf [Follman 1999](#)). If more than one study was available for imputation, we selected the largest study, unless this choice would lead to inconsistencies with the results in the original study (e.g. when the authors reported no significant difference, but the imputed data would change this). In that case the second largest study was taken.

Data synthesis

We computed pooled estimates of the treatment effect and the pooled 95% confidence intervals (CI), combining parallel and cross-over studies ([Elbourne 2002](#)). For cross-over studies we used

the results of paired analyses, extracting treatment effect, standard error and within patient correlation between DSCG and placebo period (ρ) from papers. When ρ was not given, we imputed this in the same way as stated above for missing standard errors. We tested for homogeneity (Dersimonian 1986). When heterogeneity was found ($P < 0.05$), we did not use the fixed-effect model to compute a pooled estimate and confidence interval, but only used the random-effects model (Dersimonian 1986). To investigate causes for heterogeneity, we evaluated the influence of study characteristics (year of publication, mean age of children, method of delivery, asthma severity of the study population, methodological quality, doses per day and duration). Assessment of asthma severity was based on the description of the study population in the papers (see 'Characteristics of included studies' table). As there was no single outcome measure available for all studies, we selected those outcomes for which at least 10 studies were available. To include as many studies as possible in the funnel plot (see below) and the meta-regression analysis, we combined various outcome measures that used a similar scale, taking the first available from overall symptom score, day wheeze, day cough, day activity and daytime asthma score.

For all study characteristics except asthma severity, we used univariate and multivariate meta-regression analysis (Fleiss 1993), weighing observations by the reciprocal of the square of the standard error of the mean difference between placebo and DSCG. Thus, all pooled outcomes are presented as weighted mean differences (WMD). Study characteristics were either entered as categorical (design, type of delivery) or as continuous (publication year, quality score, etc.). For asthma severity, we used the asthma score in the placebo group (or period) as study characteristic. Because this measurement is subject to measurement error as much as the outcome variables are, ordinary regression analysis is inappropriate, as this technique only assumes measurement error in the outcome variable. Therefore, we used an analysis technique called functional relationships (Nagelkerke 1992) to evaluate the influence of asthma severity of the study population on the outcome for cough, wheeze and overall symptom score.

We performed all analyses using SPSS version 10 for the initial review.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses when outcome data were available from at least 10 studies, using the following characteristics for subgroup identification: asthma severity (moderate versus severe), health care settings (hospitalised/institutionalised versus other settings), type of delivery (nebulised versus other), age (using a mean age of five years as the cut-off point), duration of follow up (using three months follow up as the cut-off point) and methodological quality (for Jadad's scoring system three points or higher versus lower; for Chalmers' summated items the 13 best studies versus the remaining studies).

To explore heterogeneity further and visualise possible publication bias, we constructed a funnel plot of the effect estimate (delta) against the precision (Egger 1995), using the same combination of outcome measures as for meta-regression analysis. The precision of a trial was defined as one divided by the standard error. The symmetry of the funnel plot was tested using a significance level of 0.10 (Egger 1997).

RESULTS

Description of studies

Results of the search

Searching the literature databases resulted in retrieval of over 3500 titles (MEDLINE: 1500; EMBASE: 1400; Cochrane Airways Group Trials Register: 850 titles). We read about 200 papers in full; 65 of these were evaluated by two authors according to a structured inclusion criteria form. The final set consisted of 24 papers, reporting on 23 studies. For one study, two papers were published reporting on different outcome measures (Yuksel 1992). Update searches were conducted in November 2006 and October 2007. These identified 181 titles, which were screened, and 10 were obtained as full papers for further assessment. None of these fulfilled our inclusion criteria, but several were added to the list of excluded studies. An updated search in October 2008 did not identify any new studies for consideration in the review. The latest search was in July 2010 and it did not return any eligible studies although two studies were added to [Characteristics of excluded studies](#).

Included studies

Most of the included studies were European (13 studies, nine of which were from the UK) or North American. Two were from Israel, three from Japan and one from Thailand. All but three papers were written in English. One study was in Norwegian (Dalene 1977), the other two in Japanese (Kobayashi 1970; Mikawa 1986).

The studies were published between 1970 and 1997. Twelve studies were published in the 1970s, eight studies in the 1980s, and four in the 1990s. Detailed information on each study is given in the table of '[Characteristics of included studies](#)'.

The age range of the children in the included studies varied considerably. Eleven studies included children not older than four years of age. In one study (Easton 1973) the age of the children was not specified. Before 1977, none of the studies included children below the age of four.

Most of the studies had a cross-over design. Four were parallel group studies. The cross-over studies typically were divided into

two periods of three or four weeks treatment, with sometimes a washout period in between. In some of the cross-over studies, the first two weeks of each period were ignored in the analysis.

In nine studies the study drugs (DSCG or placebo) were nebulised. Nine studies used dry powder in capsules, most often with the Spinhaler as device, but sometimes without a device being mentioned. In five studies the drugs were administered as aerosols with a spacer and sometimes a facemask.

In several papers it was not clear whether and what concurrent medication was permitted during the trial. We included these studies. Compliance with the therapy regimen was only discussed in a minority of papers.

Most of the studies were carried out in a hospital setting, usually with outpatients. For several studies, no information about the setting could be found. Based on the authors' affiliations, we assumed that these were hospital outpatients. In these cases we have added a question mark after 'hospital outpatients' in the table of study characteristics. Only one study recruited patients in general practice (Tasche 1997).

Regarding asthma severity, most of the studies included children that would be classified as having moderate or severe asthma by current standards (e.g. GINA 2005). Many children had one or more hospital admissions for asthma in the past. The three studies with probably the largest proportion of mild asthmatic children were Edmunds 1980; Furfaro 1994 and Tasche 1997.

The size of the trials varied between 10 and 232 participants. Only two trials included more than 100 children (Mikawa 1986; Tasche 1997). As can be expected, the parallel-group trials had larger patient groups than the cross-over trials (parallel group trials had on average 131 participants versus 26 for cross-over studies). Altogether, the 23 studies included 1026 participants.

The length of the period during which the children used either active medication or placebo in the trials varied from three weeks to 26 weeks. For 15 studies (of which 14 had a cross-over design), this was three or four weeks, while only two studies had a duration of over 10 weeks (Cogswell 1985; Tasche 1997).

Several study characteristics were strongly correlated. Dose (cor-

rected for type of delivery), method of delivery, year of publication, age of children and length of treatment period showed Pearson correlations up to 0.75.

The variety of outcome measures on which data were reported was large. Likewise, for most outcome measures only few studies reported comparable data. The outcome measures that were reported most often were asthma scores (10 studies), daytime wheeze scores (10 studies), daytime cough scores (nine studies) and bronchodilator use (10 studies). Several studies reporting on hospital admittance and steroid use provided insufficient information to be included in the pooled results.

Excluded studies

Excluded studies were either not blinded, not randomised, not placebo-controlled, did not concern the appropriate age group, or investigated the effectiveness of DSCG in exercise induced asthma. One study (Kraemer 1993) was misclassified and hence erroneously included in the first version of the review: this trial was removed from this update (see 'Characteristics of excluded studies').

Risk of bias in included studies

See: table 'Characteristics of included studies'.

The methodological quality, as assessed by two scoring methods, varied considerably (see Table 1; Table 2). Only one study attained the maximum score of five points on the Jadad list (Mikawa 1986). The proportion of items fulfilled on Chalmers's list varied between 24 and 79% (mean 44% (SD 11.9)). Of the papers reporting cross-over studies, only few stated explicitly that the sequence of both treatments had been randomised. In the analysis, we assumed they were.

When updating the review in 2007, 'Risk of Bias' tables were produced, and a summary table was added to this review (Figure 1). For further explanation of this table, see the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 8 (Higgins 2008).

Figure 1. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Bertelsen 1986	?	?	+	+	?	?
Cogswell 1985	?	+	+	+	-	?
Collins 1971	?	+	+	+	-	?
Dalene 1977	?	?	+	-	?	?
Easton 1973	?	?	+	-	?	?
Edmunds 1980	?	?	+	?	?	?
Furfaro 1994	+	?	+	-	+	?
Geller 1982	?	?	+	-	?	?
Geller 1983	?	?	+	-	?	?
Glass 1981	?	?	+	-	?	?
Henry 1984	?	?	+	?	-	?
Hiller 1975	?	+	+	-	?	?
Hiller 1977	?	+	+	?	?	?
Hyde 1970	?	+	+	+	+	?
Kobayashi 1970	?	?	+	+	?	?
Limburg 1971	?	?	+	+	+	?
Matthew 1977	?	?	+	?	?	?
Mikawa 1986	?	+	+	+	+	?
Shioda 1970	?	?	+	+	?	?
Smith 1970	+	?	+	?	?	?
Tasche 1997	?	+	+	+	-	?
Tuchinda 1974	?	?	+	+	?	?
Yuksel 1992	?	?	+	+	?	?

For several items (sequence generation, allocation concealment, selective reporting and other sources of bias), only few studies provided a clear answer. The proportion of question marks (for which the study reports do not provide enough information) is high. Blinding was considered to be adequate for all studies, which is no surprise, as this was an inclusion criterion. Several studies inadequately reported on incomplete outcome data or reported selectively. None of the studies attained the maximum score for 'withdrawals', and 20 of the 23 studies scored less than 50% on this item (Table 1).

Effects of interventions

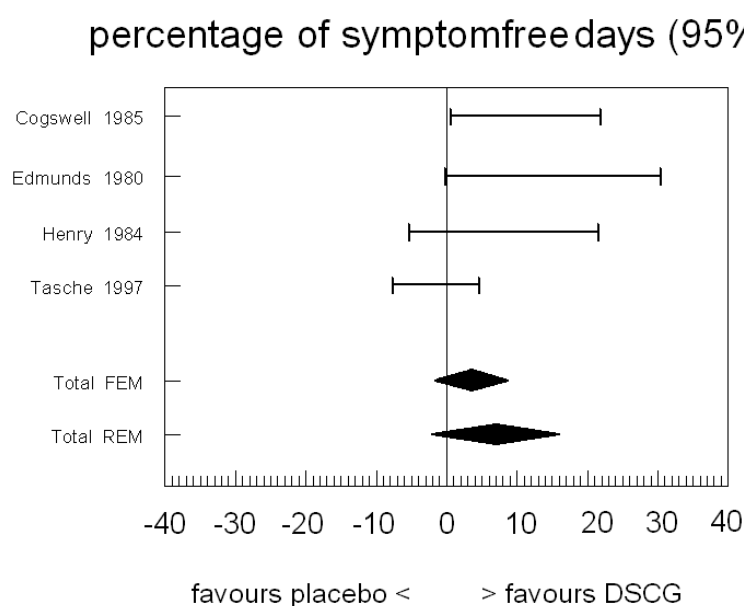
Study outcomes have been gathered into Additional tables 3 to 19 and summarised in Table 20. The tables give pooled point estimates for the difference between DSCG and placebo (i.e. DSCG

minus placebo), and confidence intervals, assuming homogeneity (fixed-effect) and heterogeneity (random-effects). Below we report the results for the outcome measures for which a considerable number of studies were available. These study outcomes are now also shown as forest plots for the primary outcome measure and all secondary outcomes with more than five contributing studies.

Symptoms

Only four studies provided results for the percentage of symptom-free days: our primary outcome measure (Figure 2; Table 3). In all but one of the studies (Cogswell 1985), the confidence interval included the point of no difference. Pooling the results revealed no significant difference between DSCG and placebo (WMD 6.76% favouring DSCG, 95% CI -2.18 to 15.70), random-effects model.

Figure 2. Forest plot of the primary outcome of the review: mean difference in % symptom-free days between sodium cromoglycate and placebo

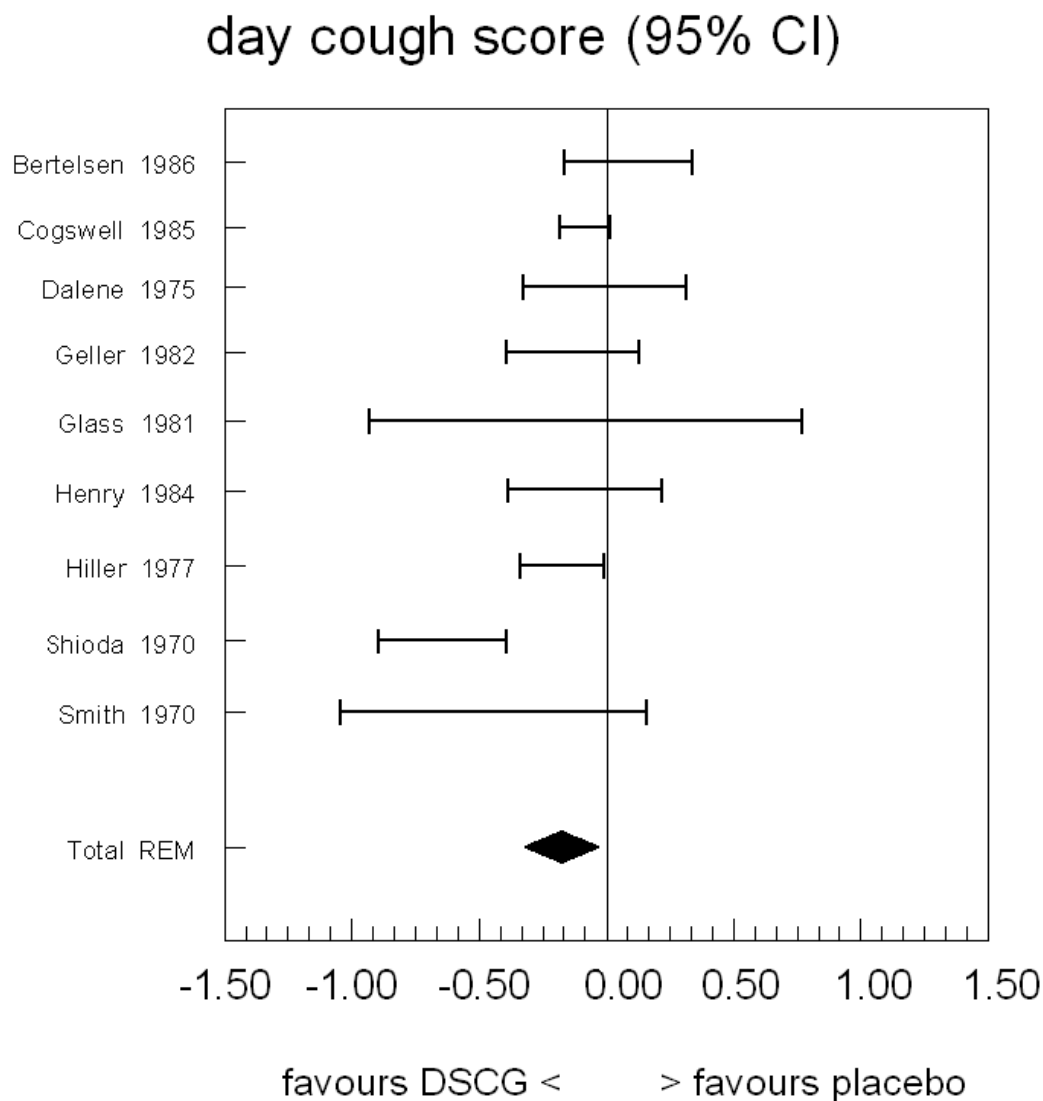


A variety of other symptom and hindrance scores was found. In tables 4 to 19 we present the results for outcome measures for which at least two studies provided data. Here we describe the results for the symptom scores with the largest number of studies: day cough score (nine studies), day wheeze score (10 studies), and overall symptom/severity score (10 studies).

For daytime cough, the difference between placebo and DSCG favoured DSCG in all but one study (Bertelsen 1986) (Figure 3; Table 4). The confidence intervals included the point of no difference for seven out of the nine studies. Pooling the results (random-effects model because of heterogeneity) did result in a statis-

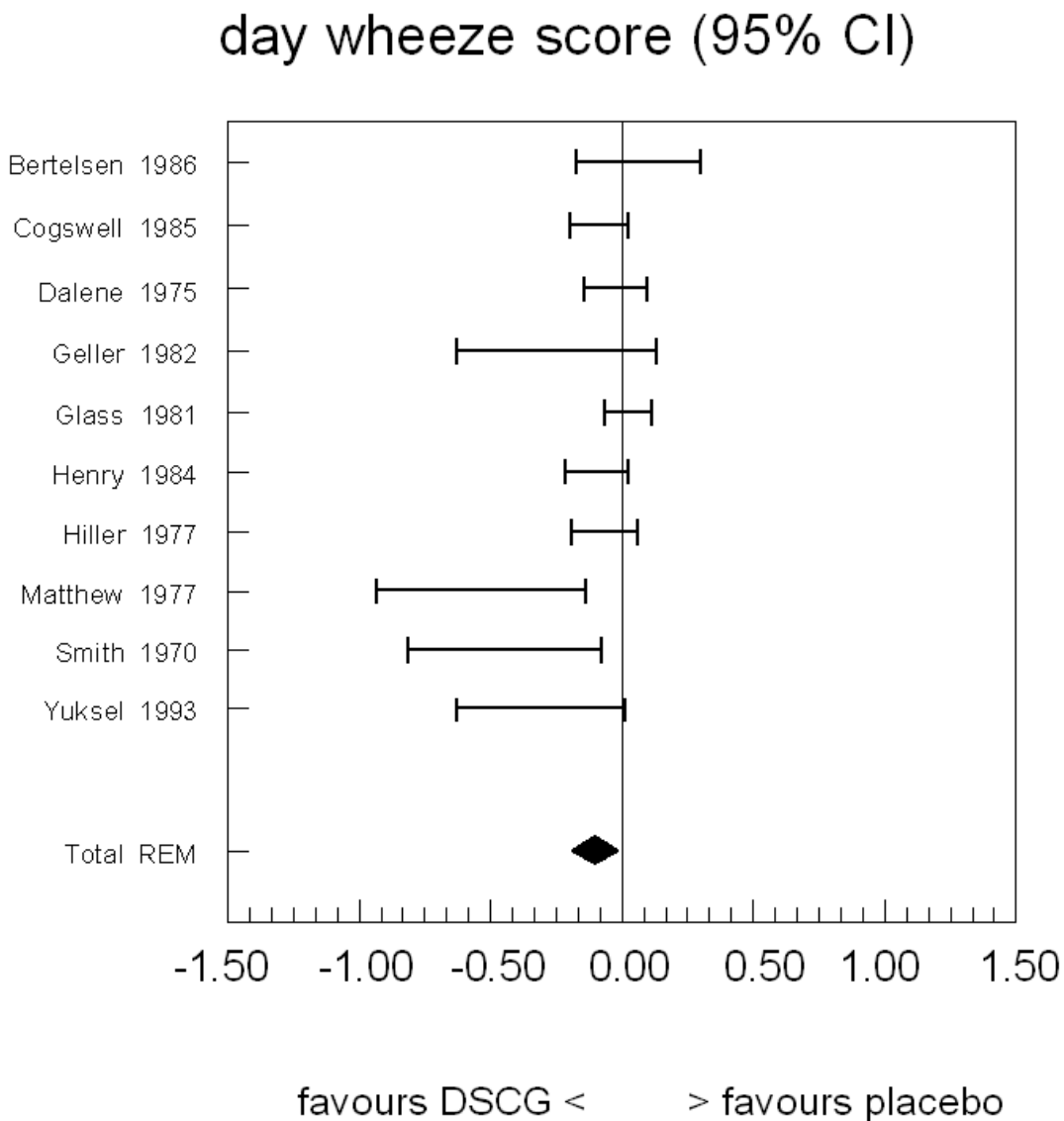
tically significant difference between placebo and DSCG favouring DSCG (WMD -0.18, 95% CI -0.32 to -0.04).

Figure 3. Forest plot of mean difference in symptom scores for day cough between sodium cromoglycate and placebo



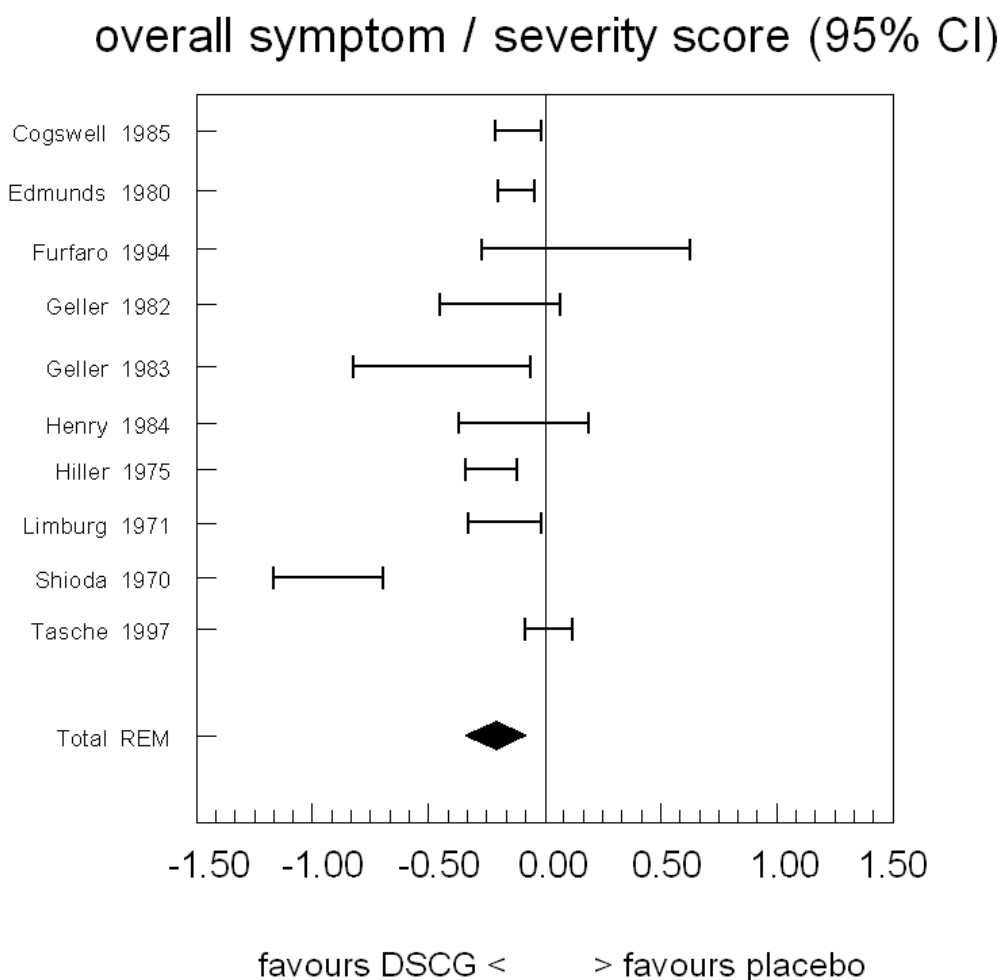
For daytime wheeze the pooled results show a small but significant difference favouring DSCG: a difference of -0.11 (WMD) on a scale of 0 to 3 (95% CI -0.19 to -0.03; random-effects model) (Figure 4; Table 5).

Figure 4. Forest plot of mean difference in symptom scores for day wheeze between sodium cromoglycate and placebo



Mean overall symptom scores favoured DSCG in direction in six out of ten studies (Figure 5; Table 6). The 95% confidence intervals of four of the studies included the point of no difference. Pooling the results (test of homogeneity rejected, hence random-effects model) showed an overall mean difference of -0.22 symptom score points (WMD), favouring the DSCG group (95%CI -0.34 to -0.09), hence statistically significant.

Figure 5. Forest plot of mean difference in overall symptoms between sodium cromoglycate and placebo

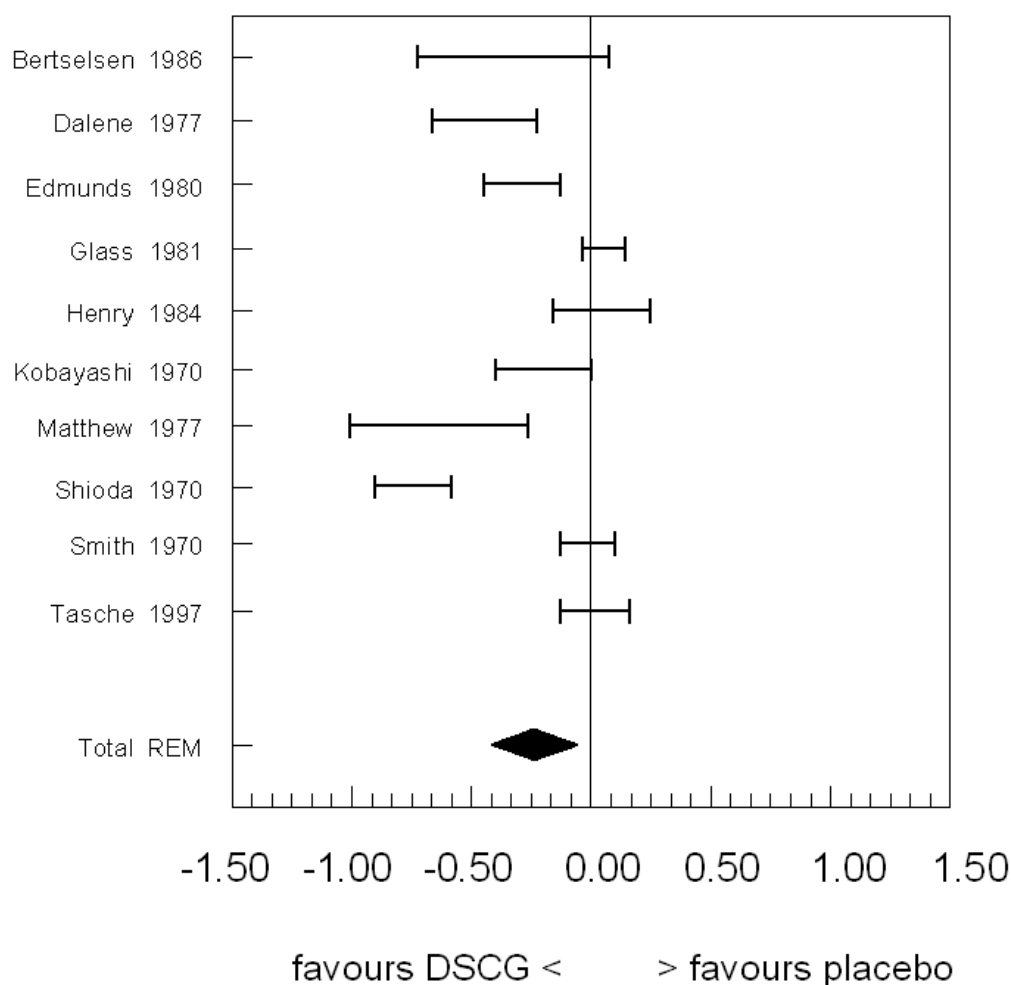


Use of other medication

The use of bronchodilators was reported in ten studies (Figure 6; Table 7). Seven of these reported a difference in favour of DSCG. Five of the studies had confidence intervals excluding the point of no difference. Pooling the data (null hypothesis of homogeneity rejected) resulted in an overall estimated difference of -0.24 daily doses (WMD) favouring the DSCG group (95% CI -0.07 to -0.42, random-effects model), which is statistically significant.

Figure 6. Forest plot of mean difference in bronchodilator use between sodium cromoglycate and placebo

bronchodilator use (doses per day) (95% CI)



Steroid use in case of exacerbations was also addressed as an outcome measure: systemic or inhaled, or sometimes unspecified. Seven studies provided these data (Table 8). Only one study (Shioda 1970) found a significant difference. The pooled results did not show a significant difference (OR 0.76, 95% CI 0.34 to 1.72).

Hospital admission

Hospital admission was reported in three studies (Table 9). None of these found a significant difference between DSCG and placebo. Pooling the results of the parallel studies did not result in a significant difference (OR 0.93, 95% CI 0.40 to 2.56).

Lung function parameters

Thirteen studies assessed lung function parameters. Eight of these reported no statistically significant difference between DSCG and placebo groups/periods, sometimes without providing exact figures. The variety of parameters, methods used, time of day tests were performed and the way they were presented made it impossible to pool data. Five of the 13 studies reported differences to be statistically significant for one or more lung function parameters (Geller 1983; Hiller 1975; Limburg 1971; Matthew 1977; Yuksel 1992).

Side effects

Twelve studies did not report on side effects (Table 10). The reported side effects of DSCG and placebo in the other 11 studies were mild and of short duration (minutes to a few days). Overall, differences between DCSG and placebo were small.

Subgroup analysis

Subgroup analyses were performed for four outcome measures: day time wheeze (10 studies), overall asthma symptom/severity score (10 studies), bronchodilator use (10 studies) and a combination of outcome measures using the same scale (19 studies, see 'Data collection and analysis'). For day time wheeze and for bronchodilator use, the differences between subgroups were either not significant or one of the groups contained only one or two studies. For the asthma symptom/severity score, the age of the children and duration of follow up showed statistically significant differences. Studies that included children with a mean age lower than five showed less effect than studies that (also) included older children

(estimate of difference between DSCG and placebo -0.06 (95% CI -0.15 to 0.02) versus -0.30 (95% CI -0.49 to -0.11), favouring DSCG, $P = 0.03$). The three studies that had at least three months follow up showed less effect than the eight shorter studies (0.04 versus 0.27, favouring DSCG, $P = 0.01$).

The combined outcome measure showed subgroup differences for way of administration of the drug, hospitalisation, age and duration of follow up. Studies that applied nebulised DSCG showed less effect than studies that used other methods of administration (0.08 versus 0.32 on a 0 to 3 point symptom scale, $P = 0.01$). Studies in hospitalised patients showed less effect than studies in other patients (0.08 versus 0.34, $P = 0.01$). Subgroup analyses for age and for duration of follow up both showed differences of the same magnitude and in the same direction for the combined outcome measure as reported above for asthma symptom/severity score.

The subgroup analyses for the above mentioned four outcome measures were also performed separately for studies with higher methodological quality (see 'Data collection and analysis' for cut-offs). Comparing the results of this subgroup of studies to the overall results revealed only minor differences, in the same direction as in our primary analysis, sometimes more in favour of the subgroup of better quality studies.

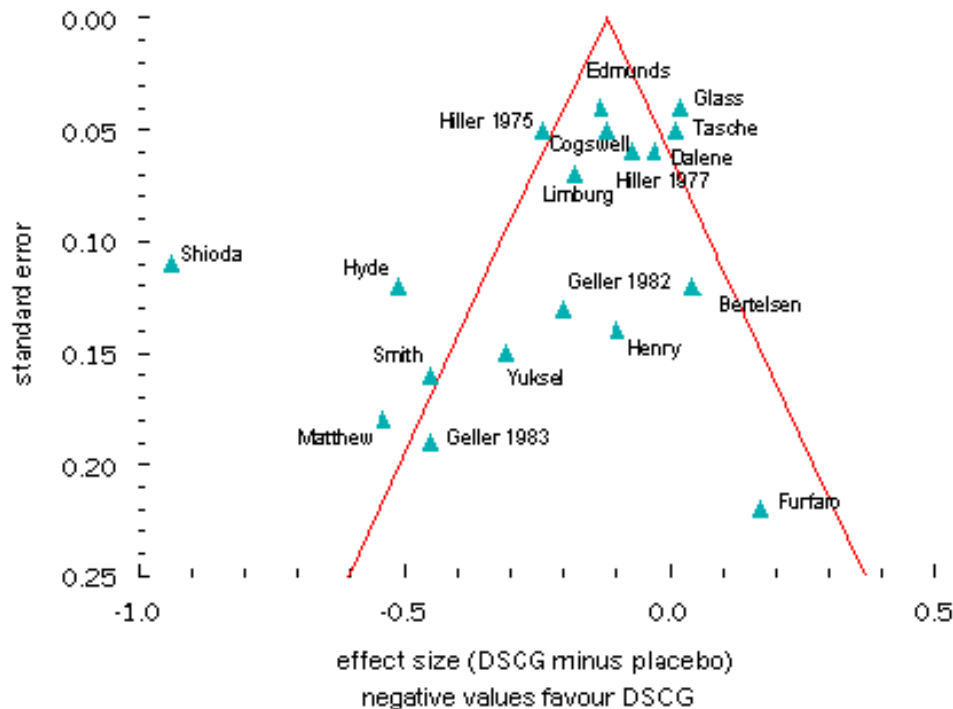
The same analyses were done excluding cross-over studies that did not take account of period effects (or did not report they did). For the asthma symptom score (five studies) the pooled difference was -0.06, with 95% CI (-0.16 to 0.03) (random-effects model). For bronchodilator use (four studies) the pooled difference was -0.05 doses (-0.12 to 0.02) (fixed-effect), the random-effects model gave -0.08 (-0.19 to 0.04), all not statistically significant. Both these outcomes are smaller than found for the whole group of studies (see Tables). For the combined outcome measures (see 'Data collection and analysis') nine studies provided data. The mean difference was -0.20, with random-effects, 95% CI -0.49 to 0.09.

Funnel plot

For the funnel plot, showing the mean difference in effect between DSCG and placebo treatment against precision of the study, we could include 19 studies. The symmetry test gave a value of -1.95 for the constant (SE 1.12, $P = 0.09$), which means that the hypothesis of symmetry was rejected. Especially imprecise (small or heterogeneous) studies with results favouring placebo were under-represented (Figure 7).

Figure 7.

Funnelplot for symptom scores (scale 0-3)



Meta-regression analysis and functional relationships

Seven study characteristics showed relationships with the (combined) outcome variable ($P < 0.25$). As only 19 studies provided data for this combined outcome measure, the power of a meta-regression analysis would be very low. Furthermore, several study characteristics were strongly related to each other (e.g. age, publication year, and method of administration of DSCG). Hence, we decided to refrain from the planned analysis.

There was no influence of placebo symptom level on study outcomes (day cough, day wheeze, overall severity score and bronchodilator use), assessed by means of functional relationships.

DISCUSSION

Summary of main results

This systematic review, involving 1026 children in 23 trials performed between 1970 and 1997, provides conflicting evidence regarding the superiority of DSCG over placebo in children with asthma. There is no evidence to support the superiority of DSCG over placebo in the percentage of symptom-free days, the main outcome of this review, although this is limited by the small number of trials reporting on this outcome.

For several secondary outcomes, especially symptom scores and bronchodilator use, we found significant group differences between DSCG and placebo, favouring DSCG. The overall treatment effect for these outcomes appears to be quite small, with a mean difference of 0.2 to 0.3 symptom score on a scale from 0 to 3 and less than $\frac{1}{4}$ puff per day for bronchodilator use. However, considering the confidence intervals of the outcome measures, a

clinically relevant effect of sodium cromoglycate cannot be excluded.

For mild persistent asthma, evidence is only available for children below the age of four. For this subgroup, we can rule out important benefit in terms of symptom scales but not in terms of symptom-free days. We cannot rule out the possibility that DSCG is of benefit in children above the age of four.

Overall completeness and applicability of evidence

Although DSCG has been advocated as maintenance treatment for mild to moderate asthma, and nowadays only for mild persistent asthma (GINA 2005), nearly all trials were hospital based, and included children with moderate to severe asthma. Three studies appear to have included a considerable proportion of children with mild asthma (Edmunds 1980; Furfaro 1994; Tasche 1997). The study by Edmunds showed positive outcomes on four outcome measures but was methodologically weak. The two other studies had negative conclusions, i.e. DSCG was not more effective than placebo. Both studies were carried out in young children (below the age of four). Studies in children above the age of five found more favourable effects than studies in children below that age.

In nine studies, the drug was administered with a nebuliser. Spinhalers were used in eight studies. Metered dose inhalers with spacer devices, nowadays the preferred method of administration for young children, were used in only two studies (Tasche 1997; Yuksel 1992). The method of administration, a critical factor in delivery of drugs to the lungs, was a predictor of outcome (combined outcome measure): studies that used nebulisation showed less effect than studies that used other methods.

The year of publication of the study and the age of the children turned out to be strongly related. In multivariate analysis, results proved to be instable, sometimes favouring age, sometimes publication year. It is impossible to disentangle these two factors: in the early days of DSCG, studies were carried out in older children and only after 1977 did studies start to include children below the age of four.

Quality of the evidence

Heterogeneity of study results is apparent for several outcome measures. The methodological quality of the studies, especially regarding sequence generation and concealment of allocation, was often impossible to assess (see 'Risk of Bias' table Figure 1), and varied considerably for other aspects.

The absence of small trials favouring placebo, as shown in the funnel plot, indicates possible publication bias. This bias is likely to result in an overestimation of the efficacy of DSCG, especially because when applying a random-effects model the small positive studies we included received a relatively large weight.

Potential biases in the review process

It has been questioned whether the (difference in) percentage of symptom-free days should be the primary outcome measure, given the fact that only a minority of studies included this (see Feedback (Edwards et al)). However, we believe that the choice of primary outcome measure should not be driven by availability, but by clinical relevance. We feel supported by national and international guidelines, where the aim of the treatment of asthma focuses on leading a normal life with few or no complaints.

Lung function parameters could not be aggregated due to incomplete reporting of data.

Agreements and disagreements with other studies or reviews

The effects of treatment with DSCG have been reviewed previously. As early as 1974 a narrative review was published in JAMA (Dykes 1974), based on data provided by the manufacturers, but giving no references to published data. Edwards 1994 examined the evidence for the anti-inflammatory action of DSCG in adults and children in a large number of controlled and uncontrolled studies but it is unclear how these were selected. Hoag 1991 summarised studies on the effect of DSCG on bronchial hyperactivity in adults and children. Schweitzer 1994 discussed the role of DSCG in children below two years of age and concluded that evidence was lacking; this conclusion was shared by Carlsen 1996. Holgate 1996 reviewed recent trials with metered dose inhalers in children and adults and discussed challenge studies, therapeutic studies, and the long-term effects of DSCG. Other reviews were Berman 1983; Carlsen 1996; Church 1985; Kuzemko 1989; Shapiro 1985; Storms 2005. None of the reviews mentioned above were systematic, assessed the methodological quality of studies or tried to quantify treatment effects. With the exception of Schweitzer 1994, all of these reviews came to conclusions in favour of DSCG.

Our group published a systematic review of inhaled DSCG as maintenance therapy in children in 2000 (Tasche 2000). The current review differs from the previous one in several respects. Seven studies that were included in the previous review were excluded in this one, either because of different exclusion criteria, especially regarding continuous use of steroids (Crisp 1974; Fox 1972; Hyde 1973; Miraglia 1982; Sly 1970), or because we initially overlooked the fact that the placebo drug contained isoprenaline and hence was not a true placebo (Silverman 1972; Smith 1968). The current review included six studies that were not included in the previous one, because of more thorough searching and the withdrawal of language restrictions (Easton 1973; Dalene 1977; Kobayashi 1970; Mikawa 1986; Smith 1970; Tuchinda 1974). Another important difference is that the previous review only considered symptom scores for cough and wheeze as outcome measures. The overall results of the previous and the first version of

the current review are similar. For the 2007 update, changing our focus for the pooled results from the tolerance interval to the random-effects model interval has slightly affected the interpretation of our results in favour of DSCG. For this update, we excluded [Kraemer 1993](#), for reasons mentioned above.

The funnel plot was similar to the one published in our earlier review (for 'wheeze'), although a different outcome was used in order to include as many studies as possible ([Figure 7](#)). As we have put forward before, when discussing our previous review ([Tasche 2000](#); [Tasche 2001](#)), publication bias may be an explanation for the asymmetry. More specifically we think it is possible that small studies that did not find a beneficial effect for DSCG may not have been submitted to journals, or may not have been published. In order to appreciate the results of this review in the context of other relevant treatments for childhood asthma, we refer to several recently published Cochrane reviews ([Adams 1999](#); [Arnold 2008](#); [Guevara 2006](#); [Gøtzsche 2008](#); [Manning 2008](#); [Seddon 2006](#); [Sridhar 2006](#)).

The possibility of publication bias could be further explored by trying to obtain information about studies that have been performed but were never published. However, since most studies we traced were published more than 20 years ago, and expecting unpublished studies to be at least as old, this does not appear to be a very promising endeavour.

This review only addressed DSCG as maintenance therapy in childhood asthma. Other studies have investigated the role of DSCG in attenuating exercise-induced bronchoconstriction, but we are unaware of a systematic review comparing DSCG to placebo for this condition. Indirect evidence from two systematic reviews in this area suggests that DSCG may be beneficial in both adults and children ([Kelly 2003](#); [Spoonner 2003](#)).

AUTHORS' CONCLUSIONS

Implications for practice

A considerable number of trials has been performed. Together, they show heterogeneous effects for DSCG compared to placebo as maintenance therapy for childhood asthma. Given the strong indication of publication bias, the small overall treatment effect, and the pooled confidence intervals including zero for our primary outcome measure and several others, we conclude that it is not justified to recommend DSCG as first line maintenance therapy in childhood asthma. This recommendation is further supported by the availability of alternatives with proven effectiveness, i.e. inhaled corticosteroids. For mild persistent asthma evidence is only available for children below the age of four. For this subgroup,

there is no good evidence that DSCG is much more effective than placebo. We cannot rule out the possibility that DSCG is of benefit in older children.

Implications for research

Given the place of DSCG in current guidelines, the lack of studies in children from age four onwards with mild persistent asthma is surprising. A large parallel study in this group, of high methodological quality and extended follow up (at least six months), could fill this gap. Preferably, such a study should not only compare DSCG to placebo, but also contain a study arm with low dose inhaled steroids. As the primary outcome measure we would recommend symptoms, either as a symptom score or as a percentage of symptom-free days. Given ongoing concern about the side effects of inhaled steroids, such a study should also address secondary outcomes like growth, adrenal function and bone density. Leukotriene-modifying drugs would be another class of drugs that could be compared to DSCG.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bertelsen 1986

Methods	DESIGN Parallel-group METHODOLOGICAL QUALITY Chalmers score 31/95; Jadad score 3 WITHDRAWALS/ DROPOUTS 5	
Participants	SETTING Hospital outpatients? AGE 1 to 4 years INCLUSION CRITERIA Recurrent wheezy bronchitis demanding treatment at least once a month during preceding winter or later N = 59	
Interventions	4 to 8 weeks baseline 10 weeks treatment 3 dd 20 mg Nebulised	
Outcomes	Day wheezing Day cough Sleep disturbance Bronchodilator use Hospital admissions	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	Quote: 'double-blind'
Incomplete outcome data addressed? All outcomes	Low risk	10 weeks: 5/59 missing, reasons provided, well balanced across groups
Free of selective reporting?	Unclear risk	Protocol not available
Free of other bias?	Unclear risk	Unclear

Cogswell 1985

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 43/91; Jadad score 4 WITHDRAWALS/ DROPOUTS 3	
Participants	SETTING Hospital outpatients? AGE 1 to 4 years INCLUSION CRITERIA Regular attacks of asthma that required at least one admission to hospital N = 27	
Interventions	4 weeks baseline, 2 x 26 weeks cross-over treatment 4 dd 20 mg nebulised	
Outcomes	% Symptom-free days Day cough Day wheeze Day activity Night cough Overall asthma severity	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Low risk	Quote: 'packaged in identical ampoules'
Blinding? All outcomes	Low risk	Quote: 'double-blind' and 'identical am- poules'
Incomplete outcome data addressed? All outcomes	Low risk	24/27 analysed, reasons for withdrawal provided, seems unbiased
Free of selective reporting?	High risk	Protocol not available, choice of one out- come (symptom free days) seems post-hoc (see Discussion)
Free of other bias?	Unclear risk	unclear

Collins 1971

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 39/94; Jadad score 2 WITHDRAWALS/ DROPOUTS 0
Participants	SETTING Hospital outpatients? AGE 7 to 17 years INCLUSION CRITERIA Severe allergic asthma, wheeze at least once a week N = 14
Interventions	2 weeks baseline 2 x 4 weeks cross-over treatment 4 dd 20 mg Spinhaler
Outcomes	Daily symptom scores Clinical assessment Lung function
Notes	Nr. of patients differs from previous version of review, due to patients on steroids Study provided no data for meta-analysis due to incomplete reporting

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Low risk	Quote: 'identical' and 'coded by manufacturer'
Blinding? All outcomes	Low risk	Quote: 'double-blind' 'physicians nor parents'
Incomplete outcome data addressed? All outcomes	Low risk	Apparently no missing data
Free of selective reporting?	High risk	No results of hemograms, BUN and SGOT
Free of other bias?	Unclear risk	Unclear

Dalene 1977

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 32/91; Jadad score 3 WITHDRAWALS/ DROPOUTS 2
Participants	SETTING Hospital outpatients? AGE 1 to 4 years INCLUSION CRITERIA Repeated episodes of virus induced asthma N = 20

Dalene 1977 (Continued)

Interventions	2 x 10 weeks Cross-over treatment 4 dd 2 ml 1% solution Nebulised	
Outcomes	Day cough Day wheeze Auscultation	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	Quote: 'double-blind'
Incomplete outcome data addressed? All outcomes	High risk	2/20 did not complete, unclear in which group
Free of selective reporting?	Unclear risk	Protocol not available, planned outcome measures unknown
Free of other bias?	Unclear risk	Unclear

Easton 1973

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 35/87 = 40%; Jadad score 2 WITHDRAWALS/ DROPOUTS 0	
Participants	SETTING Hospital outpatients? AGE Children of unspecified age INCLUSION CRITERIA Daily extrinsic asthma, stable symptoms, total blood eosinophil counts > 500 cells/cu mm N = 25	
Interventions	Baseline period unspecified 2 x 3 weeks cross-over treatment 4 dd 20 mg capsule	
Outcomes	Total eosinophil count	

Easton 1973 (Continued)

Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	Quote 'double-blind' and 'identical placebo'
Incomplete outcome data addressed? All outcomes	High risk	One patient seems missing from figure. Not mentioned in text
Free of selective reporting?	Unclear risk	Protocol not available
Free of other bias?	Unclear risk	Unclear

Edmunds 1980

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 29/91; Jadad score 2 WITHDRAWALS/ DROPOUTS 0	
Participants	SETTING Hospital outpatients? AGE 5 to 15 years INCLUSION CRITERIA Perennial asthma N = 30	
Interventions	3 x 4 weeks (incl. additional treatment) Cross-over 4 dd 1 capsule	
Outcomes	Symptom score % Symptom-free days	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned

Edmunds 1980 (Continued)

Blinding? All outcomes	Low risk	Quote: 'double-blind'
Incomplete outcome data addressed? All outcomes	Unclear risk	N of results is unclear
Free of selective reporting?	Unclear risk	Protocol not available, planned outcome measures unknown
Free of other bias?	Unclear risk	Unclear

Furfaro 1994

Methods	DESIGN Parallel-group METHODOLOGICAL QUALITY Chalmers score 56/95; Jadad score 4 WITHDRAWALS/ DROPOUTS 6	
Participants	SETTING Outpatients referred to pulmonary clinic AGE 0 to 1 years INCLUSION CRITERIA Chronic pulmonary symptoms for at least one month and wheezing documented by a physician + symptoms in baseline period N = 37	
Interventions	3 weeks baseline, 6 weeks treatment 3 dd 40 mg nebulised	
Outcomes	Symptom score	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Table of random numbers
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	Quote: 'double-blind'
Incomplete outcome data addressed? All outcomes	High risk	3 parental withdrawn, 3 poor compliance, group assignment of these children unclear
Free of selective reporting?	Low risk	Comprehensive listing of outcome measures
Free of other bias?	Unclear risk	No details

Geller 1982

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 34/91 = 37%; Jadad score 4 WITHDRAWALS/ DROPOUTS 5
Participants	SETTING Hospital outpatients? AGE 0 to 2 years INCLUSION CRITERIA Frequent troublesome wheezy bronchitis despite regular bronchodilator therapy + symptoms in baseline period N = 49
Interventions	2 weeks baseline 2 x 4 weeks cross-over treatment 4 dd 2 ml nebulised
Outcomes	Symptom score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	Quote: 'double-blind', 'matching placebo'
Incomplete outcome data addressed? All outcomes	High risk	44/49 analysed, 'one withdrawn while failing to improve during placebo period'
Free of selective reporting?	Unclear risk	Protocol not available
Free of other bias?	Unclear risk	Unclear

Geller 1983

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 41/90; Jadad score 4 WITHDRAWALS/ DROPOUTS 5
Participants	SETTING Hospital outpatients? AGE 4 to 13 years INCLUSION CRITERIA Moderately severe or severe extrinsic asthma for at least 12 months, not taken DSCG or steroids for at least 6 months before trial N = 48

Geller 1983 (Continued)

Interventions	2 weeks baseline 2 x 6 weeks treatment 4 dd 2 mg aerosol	
Outcomes	Symptom score Asthma severity score Lung function Patients', parents' and physicians' preferences	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	Quote: 'double-blind'
Incomplete outcome data addressed? All outcomes	High risk	43/48, 5 withdrawn, 'one failed to improve on placebo'
Free of selective reporting?	Unclear risk	Protocol not available, planned outcome measures unknown
Free of other bias?	Unclear risk	Unclear

Glass 1981

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 29/94; Jadad score 2 WITHDRAWALS/ DROPOUTS 0	
Participants	SETTING Hospital outpatients? AGE 1 to 4 years INCLUSION CRITERIA Poor control of asthma under routine treatment N = 16	
Interventions	4 weeks baseline, 3 x 8 weeks cross-over treatment incl. additional study arm 4 dd 20 mg nebulised	
Outcomes	Cough Wheeze Activity Sleep disturbance	

Glass 1981 (Continued)

	Additional treatment, Hospital admission Parental preference	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	Quote: 'double-blind'
Incomplete outcome data addressed? All outcomes	High risk	Tables seem to be based on fewer than 16 children (first sentence Results)
Free of selective reporting?	Unclear risk	Protocol not available, planned outcome measures unknown
Free of other bias?	Unclear risk	Unclear

Henry 1984

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 23/94; Jadad score 2 WITHDRAWALS/ DROPOUTS 3
Participants	SETTING Hospital outpatients? AGE 0 to 1 years INCLUSION CRITERIA Suffered from recurrent attacks of wheezing, asthma considered troublesome by paediatricians and parents N = 23
Interventions	2 weeks baseline, 3 x 8 weeks cross-over treatment incl. additional study arm 3 dd 20 mg nebulised
Outcomes	Wheeze Cough % Symptom-free days
Notes	Number of withdrawals probably higher
<i>Risk of bias</i>	

Henry 1984 (Continued)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	Quote: 'double-blind'
Incomplete outcome data addressed? All outcomes	Unclear risk	20/23 analysed, unclear whether withdrawal was related to outcome
Free of selective reporting?	High risk	Biased description of favourable results in some individual patients (p. 56)
Free of other bias?	Unclear risk	Unclear

Hiller 1975

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 44/87; Jadad score 4 WITHDRAWALS/ DROPOUTS 2	
Participants	SETTING Hospital outpatients? AGE 9 to 13 years INCLUSION CRITERIA Chronic perennial asthma, symptoms inadequately controlled by DSCG and bronchodilators N = 11	
Interventions	4 x 1 month cross-over treatment, including 2 additional treatment arms 4 dd 20 mg Spinhaler	
Outcomes	Daily symptom scores Clinical assessment Additional medication	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Low risk	Quote: 'packed and coded by manufacturers'

Hiller 1975 (Continued)

Blinding? All outcomes	Low risk	Quote: 'double-blind'
Incomplete outcome data addressed? All outcomes	High risk	2/23 withdrawn because of severe symptoms
Free of selective reporting?	Unclear risk	Protocol not available, planned outcome measures unknown
Free of other bias?	Unclear risk	Unclear

Hiller 1977

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 34/87; Jadad score 3 WITHDRAWALS/DROPOUTS 0	
Participants	SETTING Hospital outpatients? AGE 2 to 4 years INCLUSION CRITERIA Frequent troublesome asthma N = 17	
Interventions	1 week baseline 2 x 8 weeks cross-over treatment 3 dd 20 mg nebulised	
Outcomes	Daily symptoms Clinical assessment Lung function	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Low risk	Quote: 'coded by manufacturers'
Blinding? All outcomes	Low risk	Quote: 'double-blind'
Incomplete outcome data addressed? All outcomes	Unclear risk	All children completed the trial, for 3 children no peak flow
Free of selective reporting?	Unclear risk	Protocol not available, planned outcome measures unknown

Hiller 1977 (Continued)

Free of other bias?	Unclear risk	unclear
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Hyde 1970

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 38/87; Jadad score 3 WITHDRAWALS/ DROPOUTS 3
Participants	SETTING Hospital outpatients? AGE 6 to 16 years INCLUSION CRITERIA Duration of asthma > 1 year, definite symptoms before inclusion N = 60
Interventions	2 x 3 weeks Cross-over treatment 4 dd 20 mg Spinhaler
Outcomes	Daily symptom scores Clinical assessment Lung function Additional treatment Eosinophil level
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Low risk	Quote: 'Labels code' (p. 450-1)
Blinding? All outcomes	Low risk	Quote: 'double-blind' and taste
Incomplete outcome data addressed? All outcomes	Low risk	57/60 completed, withdrawals due to failure to cooperate or keep adequate records
Free of selective reporting?	Low risk	All outcomes seem to have been addressed
Free of other bias?	Unclear risk	unclear

Kobayashi 1970

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 45/90; Jadad score 3 WITHDRAWALS/DROPOUTS 7
Participants	SETTING Hospital outpatients AGE 6 to 15 years INCLUSION CRITERIA Moderate to severe asthma N = 37
Interventions	1 to 2 weeks baseline 2 x 4 weeks cross-over treatment 3 dd 20 mg Spinhaler
Outcomes	Daily symptom score Physician's and patient's impression
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	Quote: 'double-blind' and 'code remained unbroken'
Incomplete outcome data addressed? All outcomes	Low risk	7/37 withdrawn, seemingly unrelated to outcome
Free of selective reporting?	Unclear risk	Protocol not available, planned outcome measures unknown
Free of other bias?	Unclear risk	Unclear

Limburg 1971

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 45/94; Jadad score 3 WITHDRAWALS/ DROPOUTS 1
Participants	SETTING Asthma centre, inpatients AGE 6 to 16 years INCLUSION CRITERIA Regular asthma symptoms N = 30

Limburg 1971 (Continued)

Interventions	2 x 4 weeks 4 dd 20 mg Spinhaler	
Outcomes	Daily symptom scores Lung function Additional treatment Eosinophilia	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	Quote: 'double-blind' and 'matching placebo'
Incomplete outcome data addressed? All outcomes	Low risk	1/30 withdrawn nothing to do with this therapy (p. 368)
Free of selective reporting?	Low risk	All outcomes seem to have been reported
Free of other bias?	Unclear risk	unclear

Matthew 1977

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 29/87; Jadad score 3 WITHDRAWALS/ DROPOUTS 1	
Participants	SETTING Hospital outpatients AGE 3 to 6 years INCLUSION CRITERIA Severe chronic perennial asthma + symptoms in baseline period N = 10	
Interventions	8 weeks baseline, 2 x 4 weeks cross-over treatment 4 dd 20 mg nebulised	
Outcomes	Daily symptom scores Clinical assessment Lung function	
Notes		

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	'double-blind' and 'placebo identical'
Incomplete outcome data addressed? All outcomes	Unclear risk	Initial number of patients unclear and probably greater than 9 for which data are reported (Nine children completed? p. 36)
Free of selective reporting?	Unclear risk	Protocol not available, planned outcome measures unknown
Free of other bias?	Unclear risk	unclear

Mikawa 1986

Methods	DESIGN Parallel-group METHODOLOGICAL QUALITY Chalmers score 43/92; Jadad score 5 WITHDRAWALS/DROPOUTS 49	
Participants	SETTING Hospital outpatients? AGE 6 to 15 years INCLUSION CRITERIA Mild to moderate asthma N = 196	
Interventions	2 weeks baseline 4 weeks treatment 4 dd 20 mg aerosol	
Outcomes	Symptom scores Side effects Patients' and parents' assessment	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned

Mikawa 1986 (Continued)

Allocation concealment?	Low risk	Quote: 'randomly allocated six in a group, key codes sealed and kept by controller'
Blinding? All outcomes	Low risk	Quote: 'double-blind' and 'matching placebo'
Incomplete outcome data addressed? All outcomes	Low risk	145/196 completed. Reasons for exclusion well described, these seem unrelated to outcome (table 1)
Free of selective reporting?	Low risk	All outcomes seem to be reported
Free of other bias?	Unclear risk	Unclear

Shioda 1970

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 42/95; Jadad score 3 WITHDRAWALS/ DROPOUTS 1	
Participants	SETTING Hospital, inpatients and outpatients AGE 6 to 15 years INCLUSION CRITERIA Perennial asthma N = 34	
Interventions	2 x 4 weeks cross-over treatment 4 dd 20 mg Spinhaler	
Outcomes	Daily symptom scores Lung function Clinical assessment Additional medication School absence	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	Quote: 'double-blind' and 'neither patients, parents nor clinicians were aware'

Shioda 1970 (Continued)

Incomplete outcome data addressed? All outcomes	Low risk	1/34 withdrawn, unrelated to outcomes (although probably a side-effect)
Free of selective reporting?	Unclear risk	Protocol not available, planned outcome measures unknown
Free of other bias?	Unclear risk	unclear

Smith 1970

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 43/92; Jadad score 4 WITHDRAWALS/DROPOUTS 3
Participants	SETTING Hospital outpatients? AGE 7 to 16 years INCLUSION CRITERIA Hay fever and pollen asthma confirmed by skin prick tests N = 18
Interventions	4 weeks 4 dd 20 mg Spinhaler
Outcomes	Daily symptom scores
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	List of random numbers
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	Quote: 'double-blind'
Incomplete outcome data addressed? All outcomes	Unclear risk	15/18 completed (368), unclear in which group
Free of selective reporting?	Unclear risk	Protocol not available, planned outcome measures unknown
Free of other bias?	Unclear risk	unclear

Tasche 1997

Methods	DESIGN Parallel-group METHODOLOGICAL QUALITY Chalmers score 75/95; Jadad score 3 WITHDRAWALS/ DROPOUTS 14	
Participants	SETTING General practice AGE 1 to 4 years INCLUSION CRITERIA Previously been prescribed asthma medication and meeting criteria for moderate asthma N = 232	
Interventions	4 weeks baseline 22 weeks treatment 3 dd 10 mg aerosol + spacer (Aerochamber) + face mask	
Outcomes	% Symptom-free days Daily symptom scores Additional medication	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Low risk	Quote: 'treatment allocation was concealed from parents, patients, GPs, research physician and nurses' (p. 1061)
Blinding? All outcomes	Low risk	Quote: 'double-blind'
Incomplete outcome data addressed? All outcomes	Low risk	167/218 completed study. Equally divided and not related to primary outcome (Fig 1)
Free of selective reporting?	High risk	All outcome measures seem to be reported
Free of other bias?	Unclear risk	unclear

Tuchinda 1974

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 49/86; Jadad score 4 WITHDRAWALS/ DROPOUTS 0	
Participants	SETTING Hospital outpatients? AGE 7 to 12 years INCLUSION CRITERIA Chronic asthma	

Tuchinda 1974 (Continued)

	N = 17	
Interventions	2 x 4 weeks cross-over treatment 4 dd 20 mg Spinhaler	
Outcomes	Perceived improvement Medication score Lung function	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	Quote: 'double-blind', 'identical in taste and color'
Incomplete outcome data addressed? All outcomes	Low risk	All patients completed the study
Free of selective reporting?	Unclear risk	No results on symptoms
Free of other bias?	Unclear risk	Unclear

Yuksel 1992

Methods	DESIGN Cross-over METHODOLOGICAL QUALITY Chalmers score 32/91; Jadad score 2 WITHDRAWALS/DROPOUTS 0
Participants	SETTING Hospital outpatients? AGE 0 to 2 years INCLUSION CRITERIA Preterm born, wheeze and/or cough 3 to 4 days/week for previous 4 weeks + symptoms for at least 3 days following respiratory infections N = 16
Interventions	2 to 3 weeks treatment 4 dd 5 mg Aerosol + face mask (coffee cup)
Outcomes	Daily symptom scores Additional treatment Lung function

Yuksel 1992 (Continued)

Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not mentioned
Allocation concealment?	Unclear risk	Not mentioned
Blinding? All outcomes	Low risk	'double-blind' and 'similarly shaped and sized cannister' (Yuksel 1993)
Incomplete outcome data addressed? All outcomes	Low risk	All 16 patients completed the study
Free of selective reporting?	Unclear risk	Protocol not available, planned outcome measures unknown
Free of other bias?	Unclear risk	unclear

Assessment of concealment of allocation for cross-over studies applies only to initial allocation.

Adequacy of washout period not taken into account because of incomplete reports.

Possible unblinding due to perceived differences were not taken into account.

Setting = ? where not clearly stated, but deducted from authors' affiliations.

dd: doses per day

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Agbayani 1984	Double dummy, no placebo arm
Anastasatu 1979	Not an RCT
Anonymous 1969	Included adults as well, but no age specific results
Arndt 1975	Not placebo-controlled
Avital 1991	Theophylline versus placebo (cross-over, double dummy), no placebo arm
Berman 1975	Partly > 18 years, no separate results for children

(Continued)

Bernstein 1972	Results for children not presented separately (except patient preference) Continuous use of steroid was allowed
Blumenthal 1988	Results for children not presented separately
Bonifazi 1985	Age 10 to 50, results for children not presented separately
Booij-Noord 1971	Results for children not presented separately DSCG not as maintenance therapy
Bruderman 1990	Not an RCT
Carrasco 1989	Results for children not presented separately
Carrà 2001	No placebo arm
Chai 1973	All children on steroids continuously
Chan-Yeung 1971	Only two children
Chyrek-Borowska 1975	Results for children not presented separately
Ciszek 1974	Results for children not presented separately
Crawford 1974	Incomplete report
Crawford 1974b	Most children on steroids continuously (281 doses of 5 mg prescribed in 30 children for 4 weeks)
Crimi 1988	Not maintenance therapy (adenosine-induced bronchoconstriction)
Crisp 1974	Steroid use was one of the selection criteria, no separate results for non-users
Croce 1995	Patients 6 to 24 years Results for children not presented separately
De Baets 1998	No placebo arm
Dickson 1969	Open study
Droszcz 1973	Ages 15 to 63 years Results for children not presented separately
Edmunds 1994	No placebo arm
Engström 1975	No placebo for asthma treatment Same data as Engström 1977

(Continued)

Engström 1977	No placebo arm
Exline 1972	Results for children not presented separately
Forster 1998	Abstract only
Fox 1972	9 patients were on regular steroids, no separate results for non-users
Friday 1973	No information on age, included patients above 18 years, no age-specific results
Fuleihan 1973	Includes both adults and children, no separate results for children
Furukawa 1999	Results for children not presented separately
Garcio Velloso 1984	No information on age
Gaur 1997	No information on blinding (possibly not blinded), no placebo Results on children not presented separately
Geller-Bernstein 198	No placebo arm
Gemiciglu 1993	Ages 15 to 46, results for children not presented separately
Glazer 1971	No information on age
Godfrey 1975	Study conducted in exercise-induced bronchoconstriction
Gomez-Orozco 1976	Not an RCT
Graber 1998	Not original, refers to Tasche 1997
Grifoni 1971	Age 5 to 63 years Results for children not presented separately
Gulyas 1984	Combined therapy, not DSCG alone
Guminski 1976	No placebo arm
Haber 1989	Patients 16 to 41 years Results for children not presented separately
Herjavec 1982	No placebo arm Results for children not presented separately
Hermance 1973	Steroid use was continued
Hobday 1970	No placebo arm (isoprenaline)

(Continued)

Hyde 1971	Not an RCT
Hyde 1973	15 of 57 children were on daily steroids Results for non-users not presented separately
Inoue 1970	No placebo arm
Irani 1972	Results for children not presented separately
Ito 1971	only one child below age of 18
Jenssen 1973	Results for children not presented separately
Johannessen 1975	Results for children not presented separately
Jones 1970	Single-blind
Kehnscherper 1993	No placebo arm
Kennedy 1969	Primary reference gives no information on age Secondary reference gives 10 patients in age range 11 to 20, no specific data
Khurana 1977	Open study
Kidner 1968	Results for children not presented separately
Kimmel 1974	Open study
Klein 1980	No placebo arm
Klein 1981	No placebo arm
Knezevic 1997	(Abstract only) No placebo arm No information on randomisation
Kotaniemi 2005	Not blinded
Kraemer 1986	DSCG single-blind
Kraemer 1987	Single-blind with respect to SCG
Kraemer 1993	Daily use of bronchodilator in both arms, irrespective of symptoms
Kuzemko 1974	Study compares 2 active treatments Placebo period not double-blind

(Continued)

Kuzemko 1977	No placebo
König 1973	Not double-blind No placebo period
Lahoz 1973	Adults
Lecks 1974	Included children > 17 years of age, probably above 18 years
Lenney 1978	Exercise induced asthma
Linehan 1970	Single-blind
Löwhagen 1985	Parallel-group trial with only 1 child
Macdonald 1979	Cromoglycate not compared to placebo
Mahashur 1981	Not double-blind, not randomised, no separate results for children
Marks 1974	Incomplete results: only patients who had benefit reported
Marshall 1969	Placebo-controlled study included both children and adults
Masood 1978	Results for children not presented separately
Matsumoto 1994	Not randomised
Mattoli 1986	Allergen-induced challenge
McLean 1973	Included children > 18 years
Mellon 1982	No placebo arm
Menardo 1998	No placebo arm
Miraglia 1981	Not an RCT
Miraglia 1982	10 of 31 children use steroids continuously, no separate results for non-users
Mitchell 1976	No placebo arm
Moeller 2009	No placebo arm
Molema 1989	Results for children not reported separately
Moran 1968	Results for children not presented separately

(Continued)

Muittari 1969	Not randomised
Munro Ford 1969	No information on age, probably adults
Naganathan 1975	37 patients age 11 to 53 years, 6 patients 11 to 20 years, no age-specific results
Ng 1977	Study compares 2 active treatments Placebo period not double-blind
Orefice 1990	Not randomised
Pesic 1975	No placebo arm
Petersen 1996	No placebo arm
Price 1995	Not blinded, no placebo
Rafinski 1977	Not an RCT
Rauber 1983	No placebo arm
Reid 1988	Results for children not presented separately
Robertson 1969	Only 1 child
Romano 1970	No information on ages Description of methods very incomplete No useful results
Sarlet 1973	Not double-blind No placebo arm
Schmidt 1973	No placebo arm
Selcow 1983	Not an RCT
Selcow 1989	Age 8 to 20 years Results for children not presented separately
Sellars 1975	Age of children > 17 years, above 18?
Shioda 1973	Overlapping data with Shioda 1970, but no data on RCT
Shiota 1984	Adults only
Shore 1971	Not an RCT
Sienra Monge 1990	Not an RCT

(Continued)

Silverman 1972	Not placebo-controlled (isoprenaline)
Sly 1970	2 of 21 children used prednisone continuously, results for non-users not presented separately
Smith 1968	Not placebo-controlled (isoprenaline)
Smith 1980	Not an RCT
So 1981	Aerosol compared to powder No placebo Ages 12 to 31
Streumer 1970	Incomplete description of methods, probably not a RCT
Thompson 1974	Age 7 to 28 years Results for children not presented separately
Toshner 1974	16 patients were on continuous steroids
Turpeinen 2010	not randomised, no placebo arm
Varsano 1983	Upper respiratory tract infections, not asthma
Viscardi 1997	Not asthma
Watanabe 1992	Not an RCT
Weinbren 1969	Isoprenaline is not placebo
Wells 1979	Not maintenance therapy Cat fur challenge
Wheatley 1981	No placebo arm
Zarkovic 1991	Open study No placebo

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Methodological quality scores according to Chalmers

Study	Selection & reject log	Randomisation & concealment	Blinding	Therap regimens	Withdrawals	Compliance	Numbers & statistics	Timing	Total score (%)
Maximum score study	6	13	23	6	7	6	24	10	95 (100%)
Bertelsen 1986	1	3	12	3	3	0	6	3	31/95 = 33%
Cogswell 1985	1	10	13	4	3	1/3	9/22	2	43/91 = 47%
Collins 1971	2	7	18	6	0	0	3	3/9	39/94 = 41%
Dalene 1977	2	2	16	4	3	1	3/20	2	32/91 = 35%
Easton 1973	1	4	17	5	1	0	4/16	3	35/87 = 40%
Edmunds 1980	0	4	14	0	1	2	6/20	2	29/91 = 33%
Furfaro 1994	3	13	13	5	4	3	11	4	56/95 = 59%
Geller 1982	1	4	16	2	3	0	6/20	2	34/91 = 37%
Geller 1983	2	6	18	3	4	1	5/19	2	41/90 = 46%
Glass 1981	0	4	14	2	0	1	6	2/9	29/94 = 31%
Henry 1984	0	0	16	3	0	0	2	2/9	23/94 = 24%
Hiller 1975	2	10	18	4	3	0	5/18	2/9	44/87 = 51%

Table 1. Methodological quality scores according to Chalmers (Continued)

Hiller 1977	0	10	14	4	3	0	2/18	1/9	34/87 = 39%
Hyde 1970	1	6	13	4	3	0	6/18	5/9	38/87 = 44%
Kobayashi 1970	2	4	16	5	3	0	13/19	2	45/90 = 50%
Limburg 1971	1	4	13	5	3	0	11/23	8	45/94 = 48%
Matthew 1977	0	4	13	4	3	0	3/16	2	29/87 = 33%
Mikawa 1986	3	4	16	5	2	0	7/21	6	43/92 = 47%
Shioda 1970	3	6	18	4	2	0	5	4	42/95 = 44%
Smith 1970	2	4	16	6	3	0	4/21	8	43/92 = 47%
Tasche 1997	6	11	20	3	6	3	21	5	75/95 = 79%
Tuchinda 1974	1	5	19	6	3	0	11/15	4	49/86 = 57%
Yuksel 1992	3	4	16	5	3	0	5/21	3/9	39/91 = 43%

“/” means denominator adapted because items non-applicable.

Table 2. Methodological quality scores according to Jadad's criteria

Study	Randomisation	Randomisation detail	Double-blind	Blinding details	Withdrawals	Total
Bertelsen 1986	1	0	1	0	1	3
Cogswell 1985	1	0	1	1	1	4
Collins 1971	0	0	1	1	0	2
Dalene 1977	1	0	1	0	1	3
Easton 1973	1	0	1	0	0	2

Table 2. Methodological quality scores according to Jadad's criteria (Continued)

Edmunds 1980	1	0	1	0	0	2
Furfaro 1994	1	1	1	0	1	4
Geller 1982	1	0	1	1	1	4
Geller 1983	1	0	1	1	1	4
Glass 1981	1	0	1	0	0	2
Henry 1984	0	0	1	0	1	2
Hiller 1975	1	0	1	0	1	3
Hiller 1977	1	0	1	1	1	4
Hyde 1970	0	0	1	1	1	3
Kobayashi 1970	1	0	1	0	1	3
Limburg 1971	0	0	1	1	1	3
Matthew 1977	1	0	1	1	0	3
Mikawa 1986	1	1	1	1	1	5
Shioda 1970	1	0	1	0	1	3
Smith 1970	1	1	1	0	1	4
Tasche 1970	1	0	1	0	1	3
Tuchinda 1974	0	1	1	1	1	4
Yuksel 1992	1	0	1	0	0	2
Yuksel 1993	1	0	1	0	1	3

Table 3. Primary outcome: percentage of symptom-free days

Study	n	Rho from paper	Rho imputed or paper	Diff (c-p)	SE paper	SE imputed or paper	95% CI left	95% CI right	CI	Imputations from
Cogswell 1985	24	0.34	0.34	11.10	5.10	5.10	0.50	21.70	-	

Table 3. Primary outcome: percentage of symptom-free days (Continued)

Edmunds 1980	30	0.25	0.25	15.00	7.50	7.50	-0.32	30.32	-
Henry 1984	20	NA	NA	8.00	NA	9.89	-5.50	21.50	Edmunds 1980
Tasche 1997	218	0	0	-1.60	3.10	3.10	-7.70	4.60	-
				Homogeneity test			Chi ² = 7.48, P = 0.06		
		Pooled results mean (95% CI)		Fixed-effect model			3.57 (-1.18 to 8.32)		
				Random-effects model			6.76 (-2.18 to 15.70)		

Rho = correlation between DSCG and placebo period (cross-over studies).

NA = not available in paper.

Table 4. Day cough score

Study	n	Rho from paper	Rho imputed or paper	Diff (c-p)	SE from paper	SE imputed or paper	95% CI left	95% CI right	CI	Imputations from
Bertelsen 1986	58	0	0	0.08	0.13	0.13	-0.17	0.33	-	
Cogswell 1985	24	NA	NA	-0.09	0.05	0.05	-0.19	0.01	-	
Dalene 1975	18	NA	NA	-0.12	NA	0.16	-0.44	0.20		Shioda 1970
Geller 1982	44	NA	0.63	-0.14	NA	0.13	-0.40	0.12		Shioda 1970
Glass 1981	14	NA	NA	-0.09	0.39	0.39	-0.93	0.76	-	
Henry 1984	20	NA	NA	-0.09	NA	0.15	-0.39	0.21		Shioda 1970
Hiller 1977	17	NA	NA	-0.18	0.08	0.08	-0.34	-0.01	-	

Table 4. Day cough score (Continued)

Shioda 1970	33	0.63	0.63	-0.65	0.12	0.12	-0.89	-0.40	-
Smith 1970	18	0	0	-0.45	0.28	0.28	-1.05	0.14	-
				Homogeneity test			Chi ² = 23.44, P < 0.001		
Pooled results: mean (95% CI)				Random-effects model			-0.18 (-0.32 to -0.04)		

NA = not available in paper.

Table 5. Day wheeze score

Study	n	Rho from paper	Rho imputed or paper	Diff (c-p)	SE from paper	SE imputed or paper	95% CI left	95% CI right	Imputations from
Bertelsen 1986	58	0	0	0.06	0.12	0.12	-0.17	0.30	
Cogswell 1985	24	NA	NA	-0.09	0.05	0.05	-0.21	0.01	
Dalene 1975	18	NA	NA	-0.03	NA	0.06	-0.15	0.09	Cogswell 1985
Geller 1982	44	NA	0.34	-0.25	NA	0.19	-0.63	0.13	Matthew 1977
Glass 1981	14	NA	NA	0.02	0.04	0.04	-0.07	0.11	
Henry 1984	20	NA	NA	-0.10	NA	0.06	-0.22	0.02	Cogswell 1985
Hiller 1977	17	NA	NA	-0.07	NA	0.06	-0.19	0.05	Cogswell 1985
Matthew 1977	8	0.26	0.26	-0.54	0.18	0.18	-0.94	-0.14	
Smith 1970	18	0	0	-0.45	0.16	0.16	-0.82	-0.08	

Table 5. Day wheeze score (Continued)

Yuksel 1993	16	0.34	0.34	-0.31	0.15	0.15	-0.63	0.01	
				Homogeneity test			Chi ² = 23.47, P = 0.01		
		Pooled results: mean (95% CI)		Random-effects model			-0.11 (-0.19 to -0.03)		

NA = not available in paper.

Table 6. Overall symptom/severity score

Study	n	Rho from paper	Rho imputed or paper	Diff (c-p)	SE from paper	SE imputed or paper	95% CI left	95% right	CI	Imputa- tions from
Cogswell 1985	24	NA	NA	-0.12	0.05	0.05	-0.22	-0.02	-	
Edmunds 1980	30	NA	NA	-0.13	0.04	0.04	-0.21	-0.05	-	
Furfaro 1994	31	0	0	0.17	0.22	0.22	-0.28	0.62	-	
Geller 1982	44	NA	0.70	-0.20	NA	0.13	-0.46	0.06		Hyde 1970
Geller 1983	46	NA	NA	-0.45	0.19	0.19	-0.83	-0.07	-	
Henry 1984	20	NA	NA	-0.10	NA	0.14	-0.38	0.18		Shioda 1970
Hiller 1975	9	NA	NA	-0.24	0.05	0.05	-0.35	-0.13	-	
Limburg 1971	27	0.67	0.67	-0.18	0.07	0.07	-0.34	-0.03	-	
Shioda 1970	33	0.70	0.70	-0.94	0.11	0.11	-1.17	-0.70	-	
Tasche 1997	218	0	0	0.01	0.05	0.05	-0.09	0.11	-	

Table 6. Overall symptom/severity score (Continued)

		Homogeneity test	Chi ² = 70.76, P < 0.001
	Pooled results: mean (95% CI)	Random-effects model	-0.22 (-0.34 to -0.09)

NA = not available in paper.

Table 7. Bronchodilator use (number of doses per day)

Study	n	Rho from paper	Rho imputed or paper	Diff (c-p)	SE from paper	SE imputed or paper	95% CI left	95% CI right	CI	Imputations from
Bertselsen 1986	58	0	0	-0.33	0.20	0.20	-0.73	0.07	-	
Dalene 1977	18	NA	NA	-0.45	NA	0.11	-0.67	-0.23		Shioda 1970
Edmunds 1980	30	0.50	0.50	-0.29	0.08	0.08	-0.45	-0.13	-	
Glass 1981	14	NA	NA	0.05	0.04	0.04	-0.04	0.14	-	
Henry 1984	20	NA	NA	0.04	NA	0.10	-0.16	0.24		Shioda 1970
Kobayashi 1970	25	NA	NA	-0.20	0.09	0.09	-0.40	0.00	-	
Matthew 1977	25	0.92	0.92	-0.64	0.16	0.16	-1.01	-0.27	-	
Shioda 1970	33	0.79	0.79	-0.75	0.08	0.08	-0.91	-0.59	-	
Smith 1970	15	0	0	-0.02	0.05	0.05	-0.13	0.10	-	
Tasche 1997	218	0	0	0.01	0.07	0.07	-0.13	0.16	-	
				Homogeneity test			Chi ² = 116.06, P < 0.001			

Table 7. Bronchodilator use (number of doses per day) (Continued)

	Pooled results: mean (95% CI)	Random-effects model	-0.24 (-0.42 to -0.07)
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NA = not available in paper.

Table 8. Steroid use (ln (OR steroid) DCSG/placebo)

Study	n	Rho from paper	Rho paper or imputed	Diff (c-p)	SE from paper	SE imputed or paper	95% CI left	95% right	CI	Imputations from
Glass 1981	14	NA	NA	-4.96	8.14	8.14	-20.91	11.00	-	
Hyde 1970	42	NA	NA	-0.69	0.88	0.88	-2.41	1.03	-	
Kobayashi 1970	25	NA	NA	-3.91	6.63	6.63	-16.90	9.08	-	
Limburg 1971	27	NA	NA	-3.61	5.66	5.66	-14.70	7.48	-	
Shioda 1970	33	NA	NA	-1.95	0.87	0.87	-3.66	-0.24	-	
Smith 1970	15	0	0	-5.40	12.92	12.92	-30.72	19.92	-	
Tasche 1997	218	0	0	-0.17	0.39	0.39	-0.93	0.59	-	
Combining parallel studies (Smith and Tasche)										
Homogeneity test							Chi ² = 0.57, P = 0.45			
Pooled results: mean (95% CI) (ln (OR))				Fixed-effect model			-0.27 (-1.09 to 0.54)			
(0 = no difference)				Random-effects model			-0.27 (-1.09 to 0.54)			
Pooled results: mean (95% CI) OR				All models			0.76 (0.34 to 1.72)			
(1 = no difference)										

NA = not available in paper.

Table 9. Hospital admittance (ln (OR hospital) DSCG/placebo)

Study	n	Rho from paper	Rho imputed or paper	Diff (c-p)	SE from paper	SE imputed or paper	95% CI left	95% CI right	Imputations from
Bertelsen 1986	58	0	0	-0.07	0.55	0.55	-1.17	1.03	-
Furfaro 1994	31	0	0	-0.07	1.46	1.46	-2.97	2.85	-
Glass 1981	14	NA	NA	NA	NA	8.14	-20.91	11.00	-
Pooling parallel studies (Bertelsen and Furfaro)									
				Homogeneity test			Chi ² = 0, P = 1.0		
				Pooled results: mean (95% CI) (ln (OR))			Fixed-effect model		
				(0 = no difference)			Random-effects model		
				Pooled results: mean (95% CI) OR			All models		
				(1 = no difference)					

NA = not available in paper.

Table 10. Side effects reported in included studies

Study ID	Side effects DCSG	Side effects placebo
Bertelsen 1986	Eczema oral (1) Cough (1)	Cough (3)
Cogswell 1985	Not mentioned	Not mentioned
Collins 1971	Bitter taste (20) Cough (11) Dry mouth (4) Dizziness (2) Nausea (2) Sore throat (0) Headache (2)	Bitter taste (13) Cough (1) Dry mouth (2) Dizziness (0) Nausea (0) Sore throat (1) Headache (0)

Table 10. Side effects reported in included studies (Continued)

Dalene 1977	Not registered	Not registered
Easton 1973	Not mentioned	Not mentioned
Edmunds 1980	Nausea, vomiting, abdominal pain, headache 5%	Nausea, vomiting, abdominal pain, headache 5%
Furfaro 1994	Not mentioned	Not mentioned
Geller 1982	Not mentioned	Not mentioned
Geller 1983	None	Throat irritation (1)
Glass 1981	Well-tolerated	Well-tolerated
Henry 1984	Not mentioned	Not mentioned
Hiller 1975	Not mentioned	Not mentioned
Hiller 1977	Not mentioned	Not mentioned
Hyde 1970	Duration mild side effect less than 5 minutes Throat irritation (4) Headache (1) Brief coughing (4) Wheezing (2)	Cough (1) Wheezing (1) Headache (1)
Kobayashi 1970	No side effects	No side effects
Limburg 1971	Cough (2)	Cough (1)
Matthew 1977	Not mentioned	Not mentioned
Mikawa 1986	Mild nausea (1)	Mild nausea (1) Mild sore throat (1)
Shioda 1970	Mild Perioral dermatitis (3) Headache (1)	None
Smith 1970	Not mentioned	Not mentioned
Tasche 1997	Mild side effects (40) Eczema mask (5) Cough after inhalation (9)	Mild side effects (33) Eczema (0) Cough after inhalation (1)
Tuchinda 1974	No side effect experienced	No side effect experienced
Yuksel 1992	Not mentioned	Not mentioned

Table 10. Side effects reported in included studies *(Continued)*

Yuksel 1993	Not mentioned	Not mentioned
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FEEDBACK

Criticism of conclusions and methods

Summary

1. The primary outcome measure, symptom free days is directionally in favour of SCG in 3 of 4 studies. The results are dominated by one study in which we doubt whether the dosage was adequate.
2. Of the 16 secondary outcome measures, 8 were statistically significant in favour of SCG. None were in favour of placebo.
3. Of the 17 outcome measures, 11 are to be found in less than 5 studies. Of the 6 outcome measures that included 5 or more studies, 4 are statistically significantly in favour of SCG. None are in favour of placebo.
4. The presentation of the results is misleading.
5. Three methods of drug delivery are included with a dose range of 1 mg 3 times daily to 40 mg 3 times daily. No account is taken of the consequences of efficacy on this dose range. There is ample evidence that 2 of the delivery systems, pMDI and nebulization may not provide an adequate dose particularly in children below the age of 5 years.
6. The diagnosis of asthma is difficult to make with confidence in children below the age of 5 years. At least half the included studies are in children in this age group. Drug delivery also presents problems in this age group.
7. A number of relevant studies have been excluded. We have identified 16 studies that should have been included. Five were excluded as they apparently included subjects over the age of 17 years. Our examination of the papers shows this either not to be the case or results for subjects below 18 years were presented separately. These studies should have been included. The exclusion of studies due to some children being on regular steroid therapy is not justified in those studies in which the steroid dose was kept fixed. If this exclusion was consistent, 2 further studies should have been excluded. It is doubtful if the exclusion of studies in which a fixed dose of bronchodilator was added to both SCG and placebo treatment arms is justified if this review is considered to be representative of SCG in childhood asthma.

Reply

We have replied to most of these criticisms before in response to letters by Edwards et al (2002), commenting on a previous version of our review, published in *Thorax*. Our conclusions are based on both the fact that the confidence interval that we a priori chose to be our guidance (the tolerance interval) does include 'no effect' for most of the outcome measures as well as the strong suspicion of publication bias, as reflected in the funnel plot.

The fact that the diagnosis of asthma is difficult in young children and drug delivery may pose problems, does not mean that doctors should not treat these children, nor does it mean that investigators should not assess the effectiveness of therapeutic options in this group of children. The protocol of our review was clear in excluding studies that included patients over the age of 17 years. In this update, we excluded the study by Kraemer et al for the reasons suggested by the authors of the criticism.

Contributors

JBL Howell, MT Stevens, AM Edwards, N Åberg, B Callaghan, S Godfrey, ST Holgate, P König, A Morikawa, D Reinhardt, B Stenius-Aarniala, JO Warner, Weinberg

Criticism of updated review, 7 July 2010

Summary

The current version of the review addresses many concerns which we submitted as a comment previously. We thank the authors for addressing our comments and producing a clearer presentation of the results of their work.

Our criticisms of this review, the previous review and earlier papers on which they were based relate to the statistical methods used, the presentation of the data the interpretation of the data and the conclusions drawn. A full account of our criticisms can be found in paper by three of us [1]. This was accompanied by two commentaries by statisticians in the same journal [2,3].

The first Cochrane review concluded that 'The evidence of the efficacy of sodium cromoglicate (DSCG) over placebo is not proven'. In the latest review, the conclusion is 'There is insufficient evidence to be sure about the efficacy of (DSCG) over placebo'. This is a justified shift in stance, but still understates the case for DSCG. Although there was no statistically significant difference between DSCG and placebo on the primary outcome (symptom-free days), seven secondary outcome variables for which data were available in four or more studies were, according to the authors, all in favour of DSCG, and six were statistically significant. Rather than providing 'conflicting evidence regarding the superiority of DSCG over placebo' we believe the review provides overwhelming evidence for the efficacy of DSCG compared to placebo. We do not believe that the authors have fully justified their choice of the primary outcome, given the low power of the of this outcome in that only four studies were included, and one study dominated these results. In one of the commentaries to our paper the author states 'it seems inappropriate to put major emphasis on the meta-analysis of a primary outcome that is reported in very few of the trials' [3] They have also not provided an evidence-based response to the criticism that the dose used in this study was probably inadequate.

The authors claim that there may be publication bias, yet this is only weakly supported by their funnel plots which are potentially subject to criticism as they include different outcome variables.

The size of the overall treatment effect is claimed to be small but should be viewed in the light of the mild symptoms experienced by the children. On-treatment mean symptom scores, where given, were less than one (on a 0-3 scale) in both DSCG and placebo treatment groups. Given the relatively low margin for improvement, the treatment effects seen are indeed relevant.

Based on the above, it is surprising that the authors conclude that 'it is not justified to recommend DSCG as first line therapy in childhood asthma' (the objective was in any case to assess maintenance therapy). The drug has established evidence of safety and efficacy in a wide number of indications, and has a role in both first line and maintenance therapy.

The authors conclude that 'a clinically relevant effect of DSCG cannot be excluded'. We suggest that this review provides strong support for the beneficial effect of DSCG over placebo in childhood asthma, particularly those over four years of age.

1. Stevens MT, Edwards AM, Howell JBL. Sodium cromoglicate: an ineffective drug or meta-analysis misused? *Pharmaceut Statist* 2007; 6: 123-137.

2. Lewis S, Deeks J. Re Sodium Cromoglicate: An Ineffective Drug or Meta-analysis Misused? *Pharmaceut. Statist.* 2007; 6: 139-140

3. Lewis JA. Comment on sodium cromoglicate: an ineffective drug or meta-analysis misused? by Stevens et al.; *Pharmaceut. Statist.* 2007; 6: 141-143

Reply

We thank Dr Edwards and colleagues for their continued interest in our review. The points raised in their comment are not new, and we have carefully considered these when updating our review. As we have already clarified in previous replies, changing the primary endpoint of our review due to its infrequent availability relative to other measurements in the studies would violate elementary methodological principles.

Contributors

A M Edwards, M T Stevens, S T Holgate, SD Anderson, JBL Howell.

Declaration of interest: AME was employed by the originators of sodium cromoglicate, Fisons Pharmaceuticals from 1974 to 1995. MTS was employed by Fisons Pharmaceuticals from 1968 to 1996. STH, SDA and JBHL have all conducted clinical trials with inhaled sodium cromoglicate in the past. None have any financial interest or connection with the current manufacturers.

WHAT'S NEW

Last assessed as up-to-date: 27 July 2010.

Date	Event	Description
17 November 2010	Feedback has been incorporated	Feedback has been received and appended to the review. The authors have responded to the feedback, but there have been no changes made to the review

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 3, 2003

Date	Event	Description
28 July 2010	New search has been performed	Literature search re-run, no new included studies found. Two new excluded studies found
7 October 2009	New search has been performed	Literature search re-run; no new studies found.
27 February 2009	Amended	Risk of bias tables completed, copy edited table of included study
25 October 2008	New search has been performed	In response to external peer review: Modified overall description of outcomes, not excluding a clinically relevant benefit. Added forest plots based on values provided in Additional tables 3-19, we could not use the forest plots provided in RevMan, as we assumed a t-distribution when calculating confidence intervals for individual studies. Yuksel 1992 and 1993 combined, as these papers refer to the same study
30 May 2008	Amended	Converted to new review format.
19 December 2007	New citation required and conclusions have changed	In response to comments by Edwards et al, one study was excluded (Kraemer (1993)). Searches performed for years 2003-2007 did not reveal any new studies, but did lead to new 'excluded studies'. Paragraph and table added on side effects as reported in included studies. Paragraph 'other reviews' in Discussion was extended. Tolerance intervals for pooled results removed.

(Continued)

		Risk of Bias tables added. Discussion rewritten.
1 November 2007	New search has been performed	Literature search re-run in November 2007

CONTRIBUTIONS OF AUTHORS

JCvdW drafted text of protocol and review.

MJAT, JHJMU and JCvdW searched papers, assessed inclusion criteria and methodological quality.

RMDB and JCvdW extracted data. RMDB performed statistical analysis.

JHJMU and JCvdW drafted the 2008 update.

All authors commented on versions of the protocol and review.

DECLARATIONS OF INTEREST

The authors were involved in a placebo-controlled trial ([Tasche 1997](#)) and in an earlier systematic review comparing DSCG and placebo ([Tasche 2000](#)). Both studies had negative conclusions.

SOURCES OF SUPPORT

Internal sources

- Department of General Practice, Erasmus MC - University Medical Center Rotterdam, Netherlands.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Asthmatic Agents [*therapeutic use]; Asthma [*drug therapy]; Cromolyn Sodium [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans